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D-80298 München
Germany

date 12 September 2008
your ref
our ref 77.68.85733

BY FACSIMILE

CONFIRMATION
OF FAX

Dear Sirs

European Patent Application No. 03745226.5 (1499343)-1216
Medvet Science Pty. Ltd.

I refer to the Communication dated 19 November 2007 in respect of the above application. I hereby request further processing of this application in accordance with Article 121 EPC.

I enclose a Fee Voucher authorising the withdrawal of the further processing fee from our Deposit Account No. 28050069. If the amount indicated is incorrect, please debit or credit our deposit account accordingly.

Zur Kasse

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Please find enclosed herewith a copy of replacement pages 59-63 comprising an amended claim set consisting of 37 claims. A copy of the former pages showing the amendments in manuscript is enclosed for the convenience of the Examiner. The amendments are made without prejudice and do not represent any abandonment of subject matter. The Applicant reserves the right to file one or more divisional applications.

The reference to inducing/agonising or inhibiting/antagonising phosphorylation has been deleted from the claims and instead the agent has been defined by reference to its technical properties.

In claims 1 and 2 , the agent is defined as an agent which "agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase". Basis for this amendment may be found on page 19, in particular at lines 9-17. Based on the same passage, new claims 10 and 23 are limited to subject matter relating to an agent which "antagonises the interaction between sphingosine kinase and a phosphorylation catalyst" and new claim 11 is limited to subject matter relating to an agent which "agonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase".

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12 September 2008
77.68.85733

- 2 -

New "medical use" claims 10 and 11 have been added based on page 29, lines 4-9 in combination with page 28, lines 18-21 (and on former "Swiss" claims 28 and 29). New claim 12 specifies the treatment of a condition characterised by inflammation or unwanted cellular proliferation based on passage bridging pages 29 to 30 in conjunction with page 28, lines 19-20. Former claims 14-19, 21-22 and 24-25 have been converted into the "medical use" format.

Some minor changes have been made to some of the other claims for consistency. Thus, former claim 17 (new claim 16) and former claim 33 (new claim 27) have been amended to refer to a phosphorylation catalyst. Former claim 18 (new claim 17) has been amended to clarify that a protein kinase is meant. Former claim 21 (new claim 19) has been amended to replace the reference to "cellular activity" with a reference to "inflammation" and former claim 22 (new claim 20) has been amended to replace the reference to cellular activity with a reference to "proliferation" based on page 28, lines 18-21. Corresponding amendments have been made to former claims 24, 25, 28 and 37 (new claims 21, 22, 23 and 30) and some clarifying amendments have been made to former claim 38 (new claim 31) and former claim 40 (new claim 32).

Former claims 46 and 47 (new claims 34 and 35) have been amended to recite the position of the mutation based on page 42, lines 18-23.

Claims 1 and 2 have been limited to an *in vitro* method. Former claims 10-13, 20, 23, 26, 27, 29, 36, 39, 42-45 have been deleted without prejudice. The remainder of the claims have been renumbered and their dependencies have been adjusted where appropriate.

The Examiner has raised a lack of clarity and support objection, alleging that the former claims related to compounds defined by reference to a desirable characteristic. The claims have been limited to an agent which agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase. Thus, only three clearly defined types of agents are recited. The specification provides on page 46 at lines 10-18 a clear test which the skilled person can use to determine if an agent has one of these specific technical features. Consequently, the skilled person is left with no doubts as to which agents fall within the scope of the present claims and which agents do not. It is therefore submitted that the enclosed claims are clear. The skilled person would appreciate that agents having the properties recited in the claims other than the specific agents exemplified in the specification could be used in the claims methods and uses, so it is submitted that the claims are supported (EPO Guidelines for Examination C III 6.5).

Under item 1.2, the Examiner has objected to the former second medical use claims, contending that they do not recite a real, defined condition to be treated. New claim 23 and 12 have now been limited to two types of conditions to be treated, namely conditions characterised by inflammation or unwanted cellular proliferation. Inflammation and unwanted cellular proliferation are features or parameters which are readily recognisable to the skilled person, or which may readily be determined. Accordingly conditions characterised by such features or

12 September 2008
77.68.85733

- 3 -

parameters may readily be recognised or determined by the skilled person. Thus, the skilled person is well aware of these conditions and so it is submitted that the second medical use claims meet the requirements of Article 84 EPC.

Under item 2, the Examiner has raised an objection to former method of treatment claims 12-27. These claims have been deleted and new medical use claims 10 and 11 have been added. Claim 10 is directed to an antagonist of the interaction between sphingosine kinase and a phosphorylation catalyst for use in therapeutically downregulating inflammation or cellular proliferation. The skilled person is well aware of conditions characterised by inflammation, such as rheumatoid arthritis, atherosclerosis and asthma (see page 31, lines 23-27), as well as conditions in which cellular proliferation needs to be down-regulated, such as neoplasms (see page 31, lines 21-23). It will be recognised also that inflammation or cellular proliferation characterise, or are associated with, a number of different medical conditions. Such conditions, as argued above, can readily be determined and recognised. It would be unduly limiting, and not appropriate, to have to recite a specific list of each and every such condition; indeed this would not be commensurate with the contribution made by this invention to the art and would not be fair to the applicant. The invention shows for the first time that phosphorylation of sphingosine kinase is required for activity and that hence by specifically agonising or antagonising this phosphorylation event, cellular activities mediated by sphingosine kinase may be up or down-regulated. As is well known to the skilled person, such cellular activities include specifically inflammation and cellular proliferation, and the skilled person would, as noted above, readily be able to recognise and determine clinical situations in which it would be of therapeutic benefit to downregulate (or indeed to up-regulate) inflammation or cellular proliferation.

Claim 11 is directed to an agonist of the interaction between sphingosine kinase and a phosphorylation catalyst, or which acts as a phosphorylation catalyst of sphingosine kinase for use in therapeutically stimulating inflammation or cellular proliferation. Arguments similar to those presented above in relation to claim 10 apply. The skilled person is well aware of medical applications in which the stimulation of inflammation is desirable, for example in the context of a vaccination protocol to enable or enhance an immune response. He is also well aware of medical applications in which the stimulation of cellular proliferation is desirable, for example to enable or enhance wound healing.

Under item 3, the Examiner has raised a lack of novelty objection based on D1, alleging that this document discloses methods of modulating sphingosine kinase functional activity with agents such as PD98059. The amended claims enclosed herewith are limited to the use of an agent which agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst, or which acts as a phosphorylation catalyst of sphingosine kinase. The Applicant submits that D1 does not disclose methods and uses according to the amended claims, because the agents of D1 do not have these properties. For example, PD98059 acts on MEK, which does not directly interact with sphingosine kinase, so PD98059 does not act as a phosphorylation catalyst of sphingosine kinase, nor as an agonist or antagonist of the interaction

12 September 2008
77.68.85733

- 4 -

between sphingosine kinase and a phosphorylation catalyst. It is therefore submitted that D1 does not anticipate the present claims. With regard to the medical use claims, it should also be noted that D1 is only concerned with *in vitro* analytical methods and no medical use of any of the agents tested in D1, let alone of an agent which agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase, is in any way suggested.

The Examiner has also raised some lack of novelty objections based on D2-D7. The Applicant submits that the enclosed claims are novel over these documents for the reasons set out below.

D2 and D5 are concerned with methods of modulating sphingosine kinase functional activity, but these documents do not teach or suggest the use of an agent which agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase. D2 relates to the use of high density lipoprotein (page 12, lines 16-17), while D5 discloses the use of N,N-dimethylsphingosine and DL-threo-dihydrosphingosine (page 24, line 21). None of these agents directly affect phosphorylation of sphingosine kinase. HDL binds to a cell surface inhibitor and the latter two agents are competitive inhibitors of sphingosine kinase. Nowhere in D2 or D5 is there any disclosure specifically of modulating sphingosine kinase activity by modulating its phosphorylation - without the knowledge (provided for the first time by the present application) that sphingosine kinase is activated by phosphorylation, there is no motivation to interfere specifically and directly in the phosphorylation of sphingosine kinase.

D3 and D4 disclose that TRAF2 and TNF activate sphingosine kinase. An association of TRAF2 with sphingosine kinase is disclosed (see D3, page 7999, column 2, lines 1 of paragraph 2), but the authors admit that it is unknown how TRAF2 activates sphingosine kinase (page 8002, column 1, paragraph 2). TNF does not directly affect the phosphorylation of sphingosine kinase (it binds to an extracellular receptor). N,N-dimethyl sphingosine kinase mentioned in D3 is, as stated above, a competitive inhibitor of sphingosine kinase and does not directly affect its phosphorylation. Thus, D3 and D4 do not disclose the use of an agent which agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase.

D6 is concerned with the role of sphingosine kinase in bradykin B₂ signalling. The authors conclude that their results suggest that a certain level of sphingosine kinase activity is required for full ERK/MAP kinase activation by this receptor. Nowhere in this article is it taught or suggested that sphingosine kinase activation is enhanced by its phosphorylation or that ERK mediates the phosphorylation of sphingosine kinase. In contrast, this article teaches that sphingosine kinase appears to be required for full ERK activation by the bradykin receptor.

D6 also discloses that the activation of sphingosine kinase by this receptor may be inhibited by the inhibitor dihydrosphingosine. This molecule is a competitive inhibitor of sphingosine kinase and does not modulate its phosphorylation. Thus, D6 does not disclose the use of an agent

12 September 2008
77.68.85733

- 5 -

which agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase.

D7 discloses that dimethylsphingosine (DMS) and the phorbol ester TPA can modulate the activity of sphingosine kinase. DMS and TPA are competitive inhibitors of sphingosine kinase and so D7 does not disclose the use of an agent which agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase.

The Examiner has provided some specific comments regarding former claims 44 and 45. These claims have been deleted, rendering the objection to these claims moot.

The Examiner has alleged that demonstrating a mechanism of action cannot confer novelty to the use of a known compound such as PD980059 for a known purpose. The present claims have been limited to an agent which agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase for use in methods of modulating sphingosine kinase activity, in particular for use in the therapeutically modulating inflammation or cellular proliferation. The claims are thus limited to a particular class of agents which directly affect phosphorylation of sphingosine kinase. Such particular agents have not previously been described for the uses claimed. It is therefore submitted that the claims do not relate to a mere discovery, but to a technical new use of a particular class of agents having the technical features defined in the claims.

As explained above, the prior art does not teach the claimed methods and uses. It is also submitted that there is no suggestion in the prior art which would lead the skilled person to arrive at the claimed invention. It is therefore submitted that the enclosed claims are inventive.

It is hoped that the Examiner will now issue a favourable report. Should any further objections arise, the Examiner is kindly asked to issue a further Examination Report. Purely as a precautionary measure, should the Examiner be minded to take a decision adverse to the Applicant, Oral Proceedings are hereby requested.

A Form 1037 follows with the confirmation of this facsimile for acknowledgement purposes.

Yours faithfully
Frank B. Dehn & Co.



Hanna Dzieglewska

Encl./br

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of modulating sphingosine kinase functional activity *in vitro*, said method comprising contacting said sphingosine kinase with an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of said sphingosine kinase wherein said agent agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or acts as a phosphorylation catalyst of sphingosine kinase.
2. A method of modulating cellular activity *in vitro*, said method comprising contacting said cell with an effective amount of an agent for a time and under conditions sufficient to modulate the phosphorylation of sphingosine kinase wherein said agent agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or acts as a phosphorylation catalyst of sphingosine kinase.
3. The method according to claim 1 or 2 wherein said sphingosine kinase is human sphingosine kinase.
4. The method according to any one of claims 1-3 wherein said phosphorylation is modulated at S²²⁵.
5. The method according to claim 4 wherein said agent binds, links or otherwise associates with S²²⁵.
6. The method according to any one of claims 1-5 wherein modulation of said phosphorylation is modulation of proline-directed protein kinase catalysed phosphorylation.
7. The method according to claim 6 wherein said proline directed kinase is ERK1, ERK2 or CDK2.

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8. The method according to claim 7 wherein said proline directed kinase is ERK2.
9. The method according to any one of claims 1-8 wherein modulation is down-regulation.
10. An agent which antagonises the interaction between sphingosine kinase and a phosphorylation catalyst for use in therapeutically downregulating inflammation or cellular proliferation.
11. An agent which agonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase for use in therapeutically stimulating cellular proliferation or inflammation.
12. The agent according to claim 10, wherein said agent is for use in the treatment of a condition which is characterised by inflammation or unwanted cellular proliferation in a mammal.
13. The agent according to any one of claims 10 to 12 wherein said sphingosine kinase is human sphingosine kinase.
14. The agent according to any one of claims 10-13 wherein said phosphorylation is modulated at S²²⁵.
15. The agent according to claim 14 wherein said agent binds, links or otherwise associates with S²²⁵.
16. The agent according to any one of claims 10-15 wherein said phosphorylation catalyst is a proline-directed protein kinase.
17. The agent according to claim 16 wherein said proline directed protein kinase is ERK1, ERK2 or CDK2.

Deleted: 10. The method according to claim 9 wherein said agent is U0126. ¶
11. The method according to claim 9 wherein said agent is PD98059. ¶
12. A method for the treatment and/or prophylaxis of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate cellular activity, said method comprising administering to said mammal an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates said cellular activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said cellular activity. ¶ ... [1]

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texts\85733\VBD claims 17... [2]
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18. The agent according to claim 17 wherein said proline directed kinase is ERK2.

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20. The agent according to claim 10 or 12-18 wherein said cellular proliferation is neoplastic proliferation, TNF-induced cellular proliferation and/or anti-apoptotic activity.

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21. The agent according to claim 10 or 12-18 wherein said inflammation is inflammatory mediator production and/or adhesion molecule expression.

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22. The agent according to claim 10 or 12-18 wherein said inflammation is associated with rheumatoid arthritis, atherosclerosis, asthma, autoimmune disease or inflammatory bowel disease.

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23. Use of an agent in the manufacture of a medicament for the treatment of a condition in a mammal, which condition is characterised by inflammation or unwanted cellular proliferation, wherein said agent antagonises the interaction between sphingosine kinase and a phosphorylation catalyst.

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24. Use according to claim 23 wherein said sphingosine kinase is human sphingosine kinase.

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25. Use according to any one of claims 23-24 wherein said phosphorylation is modulated at S²²⁵.

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26. Use according to claim 25 wherein said agent binds, links or otherwise associates with S²²⁵.

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27. Use according to any one of claims 23-26 wherein said phosphorylation catalyst is

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a proline-directed protein kinase.

28. Use according to claim 27 wherein said proline directed kinase is ERK1, ERK2 or CDK2.

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29. Use according to claim 28 wherein said proline directed kinase is ERK2.

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30. Use according to claim 23-29 wherein said inflammation is induced by TNF.

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31. Use according to claim 23-29 wherein said condition is a neoplastic condition.

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32. Use according to claim 23-30 wherein said inflammation is inflammatory mediator production and/or adhesion molecular expression.

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33. Use according to claim 23-30 or 32 wherein said inflammatory condition is rheumatoid arthritis, atherosclerosis, asthma, autoimmune disease or inflammatory bowel disease.

34. An isolated sphingosine kinase variant comprising a mutation at one or more of S¹⁴⁸, S¹⁸¹, Y¹⁸⁴, S²²⁵ or T²⁵⁰, wherein said variant exhibits ablated or reduced phosphorylation capacity relative to wild-type sphingosine kinase or a functional derivative, homologue or analogue thereof.

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35. An isolated sphingosine kinase variant comprising a mutation at one or more of S¹⁴⁸, S¹⁸¹, Y¹⁸⁴, S²²⁵ or T²⁵⁰, wherein said variant exhibits enhanced or up-regulated phosphorylation capacity relative to wild-type sphingosine kinase or a functional derivative, homologue or analogue thereof.

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36. The isolated variant of claim 34 wherein said variant comprises an amino acid sequence with a single or multiple amino acid substitution and/or deletion of amino acid S²²⁵.

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37. The isolated variant of claim 36 wherein said substitution is a Ser²²⁵ Ala substitution.

10. The method according to claim 9 wherein said agent is U0126.

11. The method according to claim 9 wherein said agent is PD98059.

12. A method for the treatment and/or prophylaxis of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate cellular activity, said method comprising administering to said mammal an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates said cellular activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said cellular activity.

13. A method for the treatment and/or prophylaxis of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate sphingosine kinase functional activity, said method comprising administering to said mammal an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates said sphingosine kinase functional activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said sphingosine kinase functional activity.

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20. The method according to any one of claims 12-19 wherein said modulation is down-regulation.

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condition and said cellular activity is

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23. The method according to claim 21 wherein said condition is an inflammatory condition and said cellular activity is the production of inflammatory mediators.

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inflammatory condition is

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26. The method according to any one of claims 20-25 wherein said agent is U0126.

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27. The method according to any one of claims 20-25 wherein said agent is PD98059.

28

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or otherwise inappropriate

11/09/2008 11:00:00

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modulates the phosphorylation of sphingosine kinase and wherein inducing or otherwise agonising said phosphorylation up-regulates said cellular activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said cellular activity

11/09/2008 11:00:00

Page 61: [11] Deleted
29. Use of an agent in the manufacture of a medicament for the treatment of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate sphingosine kinase activity, wherein said agent modulates the phosphorylation of sphingosine kinase and wherein inducing or otherwise agonising said phosphorylation up-regulates said sphingosine kinase activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said sphingosine kinase activity.

11/09/2008 11:00:00

30

Page 62: [12] Deleted
36. Use according to any one of claims 28-35 wherein said modulation is down-regulation.

11/09/2008 11:02:00

37

Page 62: [13] Deleted

11/09/2008 11:02:00

and said cellular activity is TNF-induced cellular proliferation and/or anti-apoptotic characteristic

Page 62: [14] Deleted

11/09/2008 11:02:00

39. Use according to claim 37 wherein said condition is an inflammatory condition and said cellular activity is the production of inflammatory mediators.

40

Page 62: [15] Deleted

11/09/2008 11:03:00

42. Use according to any one of claims 36-41 wherein said agent is U0126.

43. Use according to any one of claims 36-41 wherein said agent is PD98059.

44. A pharmaceutical composition comprising an agent, which agent modulates phosphorylation of sphingosine kinase, together with one or more pharmaceutically acceptable carriers and/or diluents when used in accordance with the method of any one of claims 1-27.

45. An agent, which agent modulates phosphorylation of sphingosine kinase, when used in accordance with the method of any one of claims 1-27.

Page 62: [16] Deleted

11/09/2008 11:03:00

46

Page 62: [17] Deleted **11/09/2008 11:03:00**
in a region of said sphingosine kinase which region comprising a phosphorylation site

Page 62: [18] Deleted

11/09/2008 11:04:00

in a region of said sphingosine kinase which region comprising a phosphorylation site